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Left Atrial Spontaneous Echo Contrast in Mitral Valve Disease: An Indicator for an Increased Thromboembolic Risk

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The incidence of left atrial spontaneous echo contrast was evaluated in 52 patients with isolated or predominant mitral valve stenosis (Group 1) and 70 other patients who had undergone mitral valve replacement (Group 2). All patients were studied by conventional transthoracic and transesophageal two-dimensional echocardiography. Spontaneous echo contrast could be visualized within the left atrium in 35 Group 1 patients (67.3%) (including 7 patients with sinus rhythm) and 26 Group 2 patients (37.1%) (all with atrial fibrillation).

Patients with spontaneous echo contrast had a significantly larger left atrial diameter and a greater incidence of both left atrial thrombi and a history of arterial embolic episodes than did patients without spontaneous echo contrast. Association between spontaneous echo contrast and left atrial thrombi and a history of arterial embolization (considered individually or in combination) showed a high sensitivity and negative predictive value. It is concluded that spontaneous echo contrast is a helpful finding for identification of an increased thromboembolic risk in patients with mitral stenosis and after mitral valve replacement.

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Left ventricular spontaneous echo contrast is a well known phenomenon in patients with an enlarged ventricle and markedly reduced left ventricular function due to aneurysm or dilated cardiomyopathy (1–4). In the left atrium, however, spontaneous echo contrast has only occasionally been noted in patients with mitral valve stenosis (5–8), and the clinical implication of this phenomenon is still unclear.

We therefore undertook an investigation to assess the incidence of left atrial spontaneous echo contrast and its clinical significance in patients with mitral stenosis and in patients after mitral valve replacement. In addition to the conventional transthoracic approach, all patients were studied by transesophageal two-dimensional echocardiography because this technique has a high diagnostic potential, particularly for the detection of lesions located in and around the left atrium (9–13).

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Methods

Study patients. The present study included two groups of patients: Group 1 consisted of 52 consecutive patients (42 women, 10 men) with isolated (27 patients) or predominant (25 patients) mitral valve stenosis documented by cardiac catheterization or echocardiography, or both. Their age ranged from 28 to 76 years (mean 56.6 ± 10.7). At the time of the study, 16 patients had sinus rhythm and 36 had atrial fibrillation; 33 patients were receiving oral anticoagulant treatment with phenprocoumon.

Group 2 consisted of 70 other consecutive patients (46 women, 24 men) ranging in age from 23 to 72 years (mean 40.6 ± 23.7) who were studied between 6 months and 10 years after mitral valve replacement with a bioprosthesis (54 cases) or a mechanical device (16 cases). In this group, 47 patients had atrial fibrillation and 23 had sinus rhythm at the time of the study. Fifty-two patients were receiving long-term oral anticoagulant therapy with phenprocoumon.

The history of all patients was carefully researched for an unequivocally documented event of arterial embolization proven by angiography or surgery (peripheral artery) or both, scintigraphy (kidneys) or computed tomography (brain) in addition to the typical clinical signs. Historical data

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were collected by detailed review of the patients' hospital records as well as by personal interview with all patients.

Control group. Sixty-six consecutive patients (43 men, 23 women) without mitral valve stenosis or mitral valve replacement and without a history of arterial embolization served as a control group. Their age ranged from 16 to 75 years (mean 46.8 ± 16.5) and the indications for the echocardiographic studies were identification or exclusion of aortic valve prosthetic malfunction (n = 12), valvular endocarditis (n = 23), aortic dissection (n = 8), mitral valve prolapse (n = 3) or congenital cardiac disease (n = 20). Sixty-one of the patients had sinus rhythm and five had atrial fibrillation.

Echocardiography. Transthoracic M-mode and two-dimensional echocardiograms were performed using a 2.25 MHz phased array transducer system; the left atrium was imaged in the various parasternal, apical and subxiphoid standard projections. Left atrial diameter was measured in the M-mode echocardiogram recorded in the parasternal long axis; measurements were made at end-systole according to the recommendations of the American Society of Echocardiography applying the leading edge method (14).

Transesophageal echocardiographic studies were performed with a 3.5 MHz phased array transducer attached to the tip of a commercially available gastroscope (Diasonics Echoscope connected to a Diasonics 3400 R sector scanner) (9–13,15,16). Patients were fasted for at least 4 h and received mild local pharyngeal anesthesia immediately before the gastroscope was inserted. Informed written consent was obtained from all patients and the investigations were carried out in the supine left lateral position without any complication. The transesophageal study usually took <5 min.

Left atrial spontaneous echo contrast was characterized by dynamic clouds of echoes curling up slowly in a circular or spiral shape within the atrial cavity; the characteristic motion pattern allows a clear differentiation from white noise echo. On the basis of its appearance, spontaneous echo contrast was subgrouped into "marked" and "mild": marked was defined as an intensive echo contrast visible at a normal gain control of the equipment throughout the entire left atrium (Fig. 1A), whereas a discrete echo contrast appearing only in some parts of the left atrium and at a high gain was considered as mild (Fig. 1B). All echocardiograms were carefully evaluated by two independent observers regarding the presence or absence of the phenomenon of spontaneous echo contrast and its classification as well as the presence of left atrial thrombi.

Cardiac catheterization and surgery. Complete left and right heart cardiac catheterization data, obtained within 3 months of the echocardiographic studies, were available in 23 patients with mitral stenosis. Cardiac output was measured using the Fick principle; the mitral valve area was calculated by the Gorlin formula. Thirty-one Group 1 patients and eight Group 2 patients subsequently underwent mitral valve replacement or reoperation. During surgery, the left atrium was carefully inspected for the presence of thrombi.

Statistical analysis. The Scheffé test, the unpaired *t* test and the chi-square test were used. The association between a history of arterial embolization or documented left atrial thrombi, or both, on the one hand, and left atrial spontaneous echo contrast, on the other hand, was analyzed by calculating sensitivity, specificity and positive and negative predictive value as follows:

$$\text{Sensitivity} = \frac{\text{TH/E with SEC}}{\text{TH/E with SEC} + \text{TH/E without SEC}},$$

$$\text{Specificity} = \frac{\text{No TH/E without SEC}}{\text{No TH/E without SEC} + \text{no TH/E with SEC}},$$

$$\text{Predictive value } (+) = \frac{\text{TH/E with SEC}}{\text{TH/E with SEC} + \text{no TH/E with SEC}},$$

$$\text{Predictive value } (-) = \frac{\text{No TH/E without SEC}}{\text{No TH/E without SEC} + \text{TH/E without SEC}},$$

where SEC = left atrial spontaneous echo contrast and TH/E = proven left atrial thrombi or a history of arterial embolization, or both. Accordingly, the association between a left atrial diameter >60 mm and a history of arterial embolization or atrial thrombi, or both, was analyzed. Furthermore, a stepwise multiple logistic linear regression (method MLR = maximum likelihood ratio) was calculated to test the association between thromboembolic risk and left atrial spontaneous echo contrast; the presence of atrial thrombi or a history of arterial embolism, or both, served as a dependent variable, whereas atrial fibrillation (yes/no), anticoagulation (yes/no), left atrial size (mm) and left atrial spontaneous echo contrast were used as independent variables.

Results

Incidence of spontaneous echo contrast. Transthoracic echocardiography revealed left atrial spontaneous echo contrast in only 1 (0.8%) of the 122 patients; this patient had undergone mitral valve replacement 3 years before the study and the left atrial diameter was 76 mm. In contrast, in the transesophageal echocardiograms, spontaneous echoes within the left atrium could be detected in 61 (50%) of the 122 patients; they were classified as "marked" in 42 (34.4%) and "mild" in 19 patients (15.6%).

Independent evaluation by the two observers resulted in only minor discrepancies concerning the classification of marked or mild echo contrast in three patients, amounting to an interobserver variability of 2.5%. There were no differ-

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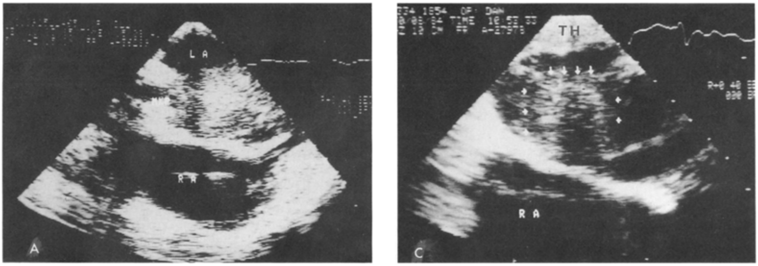


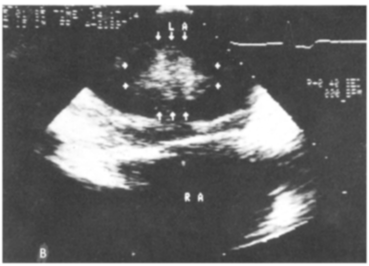


Figure 1. Transesophageal echocardiograms. **A,** Patient with a mitral valve prosthesis (MKP) and marked spontaneous left atrial (LA) echo contrast. **B,** Patient with mitral stenosis and mild spontaneous left atrial (LA) echo contrast (**arrows**). **C,** Patient with a thrombus (TH) and marked spontaneous echo contrast (**arrows**) within the left atrium. RA = right atrium.

ences regarding presence or absence of spontaneous echoes, and in the three patients with differences in classification a consensus was reached by reviewing the echocardiographic recordings.

The incidence of spontaneous echoes in the left atrium was significantly higher in Group 1 (67.3%) than in Group 2 (37.1%) ($p < 0.001$). In addition, in Group 1, spontaneous echoes were seen in seven patients with sinus rhythm, whereas in Group 2 all patients with spontaneous echoes had atrial fibrillation (Table 1). Left atrial spontaneous echo contrast could not be detected in any of the 66 control patients without mitral stenosis or a valve prosthesis.

Association of left atrial spontaneous echo contrast with thrombi and history of embolization (Tables 2 and 3). In 11 patients, left atrial thrombi were echocardiographically visualized and subsequently proved by surgery; 25 patients had a history of documented arterial embolization to the brain (n = 16), kidneys (n = 4) and limbs (n = 8) (including 3 patients with repetitive events). Sixteen patients had had the embolic events within 1 year and five patients within 2 years of the echocardiographic study. In four patients, embolism had been documented 7, 11, 13 and 14 years, respectively, before the echocardiographic investigation; these four patients had subsequently undergone consequent anticoagulant therapy. Only four patients without detectable atrial spontaneous echoes had a history of arterial embolization, and no patient without spontaneous echoes was found to have thrombus within the left atrium. The majority of patients with thrombus or a history of embolization, or

Table 1. Left Atrial Spontaneous Echo Contrast in 52 Patients With Mitral Stenosis (Group 1) and 70 Patients After Mitral Valve Replacement (Group 2)

	Group 1 no. (%)		Group 2 no. (%)	
Spontaneous echo contrast				
Present	35 (67.3)	(SR 7)	26 (37.1)	
Marked	21 (40.4)	(SR 3)	21 (30.0)	
Mild	14 (26.9)	(SR 4)	5 (7.1)	
Absent	17 (32.7)	(SR 9)	44 (62.9)	(SR 23)

SR = number of patients with sinus rhythm; the remaining patients had atrial fibrillation.

Table 2. Association Between Spontaneous Echo Contrast and Left Atrial Thrombi or History of Arterial Embolization, or Both, in 122 Patients

Spontaneous Echo Contrast	Group 1 (n = 52)				Group 2 (n = 70)			
	n	Thrombi	Embolism	Thrombi and/or Embolism	n	Thrombi	Embolism	Thrombi and/or Embolism
Present	35	8	13	19	26	3	8	10
Marked	21	6	9	13	21	3	7	9
Mild	14	2	4	6	5	—	1	1
Absent	17	—	2	2	44	—	2	2

both, were in the group with marked spontaneous echoes; a typical example is shown in Fig. 1 C.

Hence, 29 (47.5%) of 61 patients with spontaneous echoes exhibited atrial thrombi or had a history of documented arterial embolization, or both, compared with only 4 (6.6%) of 61 patients without spontaneous echoes ($p < 0.0005$). For the association between left atrial spontaneous echo contrast and the incidence of left atrial thrombi or a history of arterial embolization, or both (considered individually or in combination), statistical analysis revealed a high sensitivity and negative predictive value, whereas specificity and positive predictive values were low (Table 3). Stepwise multiple logistic linear regression analysis comparing spontaneous echo contrast, atrial fibrillation, anticoagulation and left atrial size concerning their value for identification of patients with an atrial thrombus or a history of arterial embolization, or both, clearly selected the spontaneous echo contrast phenomenon as the only independent predictor ($p < 0.0001$) (adequacy of fit [chi square] $p = 0.668$).

Influence of anticoagulation. Of 85 patients studied while on long-term anticoagulant therapy, 46 (54.1%) showed spontaneous echo contrast and 39 (45.9%) did not. Thirty-seven patients were not on anticoagulant therapy at the time of the echocardiographic study; in 15 (40.5%) of them, spontaneous echoes could be identified. There was no significant difference between patients treated with and without anticoagulants with regard to presence or absence of spontaneous echo contrast.

Left atrial diameters. Patients with spontaneous echo contrast (marked and mild) had a significantly larger left atrial diameter than did those without (Fig. 2 and 3, Table 4); the differences between patients with marked and mild spontaneous echo contrast, however, were statistically insignificant. Although there was considerable overlap among the various groups, the upper limit of left atrial diameter for patients without spontaneous echo contrast was approximately 60 mm; 40 (65.6%) of the 61 patients with spontaneous echoes had an atrial diameter >60 mm compared with only 1 patient (1.6%) among those without spontaneous echo contrast.

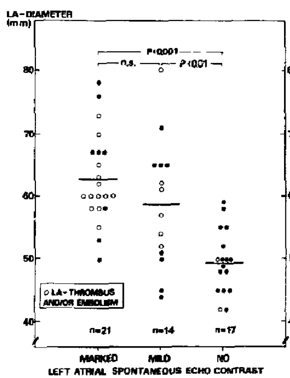
Patients with atrial thrombi or a history of arterial embo-

Table 3. Predictive Value of Association Between Left Atrial Spontaneous Echo Contrast and Left Atrial Thrombi and/or History of Arterial Embolization

	Thrombi	Embolism	Thrombi and/or Embolism
Present with SEC (n)	11	21	29
Absent with SEC (n)	50	40	32
Present without SEC (n)	0	4	4
Absent without SEC (n)	61	57	57
Sensitivity (%)	100	84.0	87.9
Specificity (%)	54.9	58.8	64.0
Pos predictive value (%)	18.0	34.4	47.5
Neg predictive value (%)	100	93.4	93.4

Neg = negative; pos = positive; present and absent = presence and absence, respectively, of thrombi and/or episodes of documented arterial embolization; SEC = left atrial spontaneous echo contrast.

Figure 2. Left atrial (LA) diameter of 52 patients with mitral stenosis (Group 1) and marked, mild or no left atrial spontaneous echo contrast. **Open circles** represent patients with a left atrial thrombus or a history of documented arterial embolism, or both; p values were obtained using the Scheffé test.



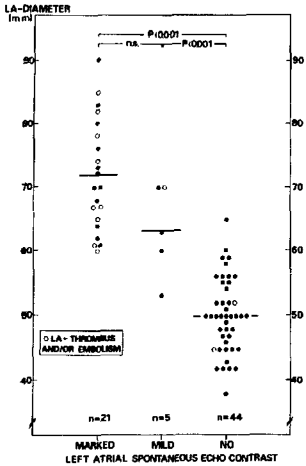


Figure 3. Left atrial (LA) diameter of 70 patients with a mitral valve prosthesis (Group 2) and marked, mild or no left atrial spontaneous echo contrast. **Open circles** represent patients with a left atrial thrombus or a history of documented arterial embolism, or both; p values were obtained using the Scheffé test.

lization, or both, had a larger left atrial diameter than did those without (62.7 ± 10.0 versus 55.6 ± 10.7 mm, $p < 0.002$). When a left atrial diameter >60 mm was chosen, this variable revealed a sensitivity of 68.8, a specificity of 70.0 and a positive and negative predictive value of 44.9 and 86.3%, respectively, for identification of patients with atrial thrombi or a history of arterial embolization, or both.

In the 66 control patients without mitral stenosis or valve prosthesis and without spontaneous echo contrast, left atrial diameter ranged between 30 and 53 mm (mean 38.7 ± 6.6).

Table 4. Left Atrial Diameter in Patients With and Without Spontaneous Echo Contrast

		Left Atrial Diameter (mm)	
Spontaneous Echo Contrast	n	Group 1 (n = 52)	Group 2 (n = 70)
Present	61	61.2 ± 8.6	70.2 ± 9.0
Marked	42	62.9 ± 7.2	71.8 ± 8.7
Mild	19	58.7 ± 19.2	63.2 ± 7.2
Absent	62	49.5 ± 5.0	50.1 ± 5.7

Values represent group means ± 1 SD.

Table 5. Hemodynamic Data of 21 Group 1 Patients With and Without Spontaneous Echo Contrast

	SEC Present (n = 13)	SEC Absent (n = 8)	p Value
Cardiac index (liters/min per m^2)	2.3 ± 0.7	2.3 ± 0.4	NS
Mitral valve pressure gradient (mm Hg)	14.8 ± 5.8	15.3 ± 6.3	NS
Mitral valve area (cm^2)	0.99 ± 0.48	0.97 ± 0.43	NS

Values represent group means ± 1 SD; NS = not significant; other abbreviations as in Table 3.

Correlation with hemodynamic data. The most relevant hemodynamic data of the 23 patients with mitral valve stenosis (Group 1) in whom cardiac catheterization was performed within 3 months of the echocardiographic study are shown in Table 5 and Fig. 4 and 5. Mean values of mitral valve pressure gradient, mitral valve area and cardiac index showed no significant differences when patients with and without spontaneous left atrial echo contrast were compared.

Discussion

Mechanism of spontaneous echo contrast. The occurrence of intravascular or intracardiac spontaneous echo contrast has been reported in patients with left ventricular aneurysm as well as with dilated cardiomyopathy (1–4). In patients with mitral valve stenosis and after mitral valve replacement, this phenomenon could be occasionally seen in the left atrium (5–8). Furthermore, spontaneous echoes were also found in the inferior vena cava of patients with constrictive pericarditis in whom they disappeared after surgery (17). And finally, in cases with aortic dissection, spontaneous echoes may be seen within the false lumen of the aorta (18). Common to all these conditions is a slow blood flow situation.

In vitro and in vivo experiments performed by Sigel et al. (19) revealed that blood within isolated vessels becomes echogenic within a few seconds up to 3 min after the onset of stasis induced by cross-clamping maneuvers. Echoes appear first near the vessel wall and disappear immediately after mechanical agitation of the blood in stasis. In addition, Sigel et al. found that the presence of fibrinogen or its products plus erythrocytes is needed to create echogenicity of static liquid blood and that this cannot be prevented by heparin. As one of the underlying mechanisms favoring the production of blood echogenicity, a rouleau formation of erythrocytes has been discussed.

Left ventricular intracavitary echoes. Comparable results were obtained by Mikell et al. (1), who studied the phenom-

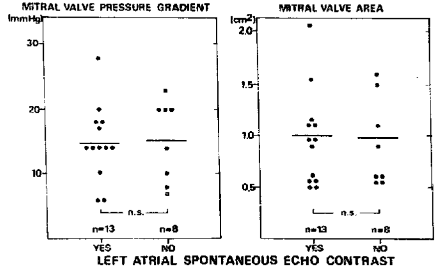
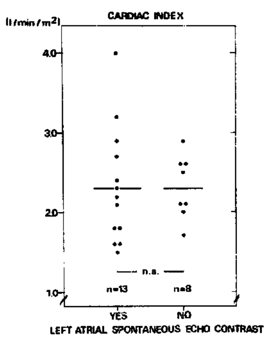


Figure 4. Mitral valve pressure gradient and area of 21 patients with mitral stenosis with (yes) and without (no) left atrial spontaneous echo contrast.

enon of dynamic left ventricular intracavitary echoes in humans as well as in dogs. All nine patients in their series who had definite evidence of left ventricular spontaneous echo contrast also showed severe apical wall motion abnormalities due either to previous anterior myocardial infarction or to congestive cardiomyopathy. In seven of the nine patients an associated apical thrombus was found. Furthermore, 7 of the 11 dogs in which an anterior myocardial infarction was created by coronary ligation and a mural left ventricular thrombus was generated by subendocardial injection of sodium ricinoleate, also showed dynamic intracavitary echoes; at postmortem, only liquid blood was found in the corresponding left ventricular area. Because of the evanescent and poorly defined border zones as well as the typical slowly moving motion pattern, the "smoke like" echoes could easily be differentiated from thrombi. In addition, Mikell et al. (1) could show that interventions influencing the contractility of the left ventricle (induction of ventricular ectopic beats, dopamine infusion) markedly altered the shape and motion of the intracavitary echoes. And finally, in an in vitro part of their studies, these investigators could provide evidence that erythrocytes and not platelets are most probably the source of blood echogenicity.

In a currently performed study in our laboratory, we observed spontaneous left ventricular echoes in patients undergoing diagnostic left ventricular stimulation; echoes appeared within seconds after induction of a rapid ventricular tachycardia and they disappeared immediately when regular sinus rhythm was reestablished.

Figure 5. Cardiac index of 21 patients with mitral stenosis with (yes) and without (no) left atrial spontaneous echo contrast.



Spontaneous Echo Contrast in Mitral Valve Disease

Previous studies. Only a few studies consider spontaneous echo contrast within the left atrial cavity. Iliceto et al. (5) found this phenomenon in 10 (3.6%) of 281 patients with mitral valve stenosis undergoing transthoracic M-mode and two-dimensional echocardiography with a 2.5 or 3.5 MHz transducer. Of seven patients in whom dynamic intraatrial echoes could be detected with a 3.5 MHz transducer, only one patient showed these echoes when restudied with a 2.5 MHz transducer. Three of the 10 patients had associated left atrial thrombi and all 10 had atrial fibrillation. After mitral valve surgery in three patients, spontaneous echo contrast was no longer visible.

Beppu et al. (8) studied 116 consecutive patients with rheumatic mitral valve disease and applied a 2.4 MHz phased array transducer system. They found smoke like echoes in the left atrium in 37 patients (31.9%); all had atrial fibrillation and had a significantly larger atrial diameter than did patients without spontaneous echo contrast. Left atrial

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thrombi were found in 13 (35.1%) of 37 patients with, and in 6 (7.6%) of 79 patients without dynamic atrial echoes. Forty patients were restudied after surgery, 20 with and 20 without preoperative smoke like echoes; 3 of them demonstrated atrial contrast postoperatively, including 2 patients without this phenomenon before surgery. All three patients developed a large left atrial thrombus within 3 weeks after operation. An additional variable studied by these authors, the calculated shear rate of the left atrial blood, was significantly lower in patients with than in those without atrial echo contrast.

Present study with esophageal echocardiography. The present study differs from previous work in that not only left atrial thrombi but also the presence or absence of embolic events in the patients' history were included in the evaluation. In addition, both transthoracic and transesophageal two-dimensional echocardiography were utilized. In >1,300 transesophageal echocardiographic studies performed in our laboratory without any complication, this method always provided a superior quality of imaging of the heart, and in particular of the left atrium, than did the transthoracic approach, including clear visualization of the left atrial appendage where thrombi are often located. Although transesophageal echocardiography, like conventional gastroscopy, is associated with some inconvenience for the patient, its superior diagnostic potential, demonstrated in many studies in recent years, justifies its use in selected patients.

Whereas transthoracic echocardiography allowed the visualization of atrial spontaneous echo contrast in only one of our study patients, this phenomenon could clearly be documented by transesophageal echocardiography in 67.3% of the patients with mitral stenosis and in 37.1% of the patients after mitral valve surgery. The difference between the two echocardiographic techniques as well as the greater incidence of dynamic intraatrial echoes in the present study compared with previous studies (5,8) is most probably due not only to the different transducer frequencies but in particular to the superior imaging quality obtained by the transesophageal approach. However, it was not the aim of the present study to obtain a reliable comparison between transthoracic and transesophageal echocardiography regarding their potential to detect atrial spontaneous echo contrast. Had this been the intention, it would have been necessary to use the same transducer frequencies in both techniques. Our study was undertaken to assess the clinical implications of left atrial spontaneous echo contrast; the transthoracic investigations were carried out by the use of a 2.25 MHz transducer system, because this frequency is still the most widely applied in adult echocardiography.

Our results clearly show that, on average, patients with spontaneous echo contrast have a significantly larger left atrial diameter than do those without spontaneous echoes; in patients after mitral valve replacement, this phenomenon is less common than in patients with mitral stenosis. However (and in contrast to the findings by Iliceto et al. [5]), it also exists postoperatively, in particular, in patients with a left atrial diameter >60 mm. In rare instances, in patients with a large atrium, spontaneous echo contrast may also be observed during sinus rhythm. However, spontaneous echo contrast was not detected in any of our 66 control patients without mitral stenosis or a prosthetic valve.

In contrast to the findings by Beppu et al. (8), in our series, the presence or absence of spontaneous echo contrast was not associated with significant differences in cardiac index, mitral valve pressure gradient and valve area. This is not difficult to explain because patients with the same cardiac output may have a completely different flow profile within the left atrium depending on the atrial size; the latter, on the other hand, is influenced by various factors other than mitral valve area alone (such as the time course of the disease and degree of associated mitral regurgitation).

Of special clinical interest is our finding that patients with spontaneous left atrial echo contrast had a significantly more frequent a history of arterial embolization and a significantly higher incidence of left atrial thrombi than did patients without this phenomenon. Although it cannot be ruled out that arterial embolization (at least in some cases) could also have been caused by reasons associated with deformed leaflets of the native or prosthetic valve or to transient arrhythmias, the association of embolization with spontaneous left atrial echo contrast revealed a high sensitivity and negative predictive value (higher than the left atrial size alone). This indicates, on the one hand, that most patients with thrombi or history of embolism, or both, could be correctly identified by the presence of spontaneous echo contrast and, on the other hand, that patients without this echocardiographic finding had a relatively low thromboembolic risk.

Conclusions. Our data indicate that left atrial spontaneous echo contrast on echocardiography may be a helpful variable in identifying increased thromboembolic risk in patients with mitral stenosis or mitral valve replacement.

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